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=> d his

     (FILE 'HOME' ENTERED AT 15:46:25 ON 16 NOV 2004)

     FILE 'EUROPATFULL, FRFULL, PATDPAFULL, PCTFULL, RDISCLOSURE, USPATFULL,
     USPAT2' ENTERED AT 15:46:54 ON 16 NOV 2004
L1          1767 S 5(W)HT?(L)(CNS(3A)(DISORDER# OR DISEASE# OR CONDITION#))
L2           518 S L1 NOT PY>=2000
L3           689 S (5(W)HT3)(5A)ANTAGONI?
L4           143 S L3(L)(CNS(3A)(DISORDER# OR DISEASE# OR CONDITION#))
L5            74 S L4 NOT PY>=2000

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 16:04:53 ON
     16 NOV 2004
L6            23 S L5
L7            10 DUP REM L6 (13 DUPLICATES REMOVED)

     FILE 'CAPLUS' ENTERED AT 16:17:08 ON 16 NOV 2004
L8             1 S US6071966/PN
                 SELECT L8 1 RN
L9            23 S E4-E120
L10            4 S L9 AND 5(W)HT?
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=> d ibib abs 1-10

L7 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 1999:763131 CAPLUS
DOCUMENT NUMBER: 132:44350
TITLE: 5-HT3 receptor antagonists
AUTHOR(S): Higgins, Guy A.; Kilpatrick, Gavin J.
CORPORATE SOURCE: PRPN CNS, F. Hoffmann-La Roche, Basel, 4070, Switz.
SOURCE: Expert Opinion on Investigational Drugs (1999), 8(12), 2183-2188
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 57 refs. The 5-HT3 receptor is a ligand-gated ion channel widely distributed in the central and peripheral nervous systems. Many selective **5-HT3** receptor **antagonists** have been developed; animal studies with such compds. suggested their potential therapeutic value in combating emesis and a wide range of **CNS diseases** including anxiety, schizophrenia, drug dependence and Alzheimer's disease. Their successful introduction as anti-emetics, with irritable bowel syndrome emerging as a further indication have partially fulfilled this initial promise. However, the CNS area has been less productive and, to date, no selective **5-HT3** receptor **antagonist** has been approved for use in a **CNS disease**.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:314042 CAPLUS
DOCUMENT NUMBER: 126:338368
TITLE: Microdialysis measurements of free drug concentrations in blood and brain
AUTHOR(S): Van Amsterdam, C.; Misslin, P.; Lemaire, M.
CORPORATE SOURCE: Drug Metabolism and Pharmacokinetics, Sandoz Pharma Ltd., Basel, CH-4002, Switz.
SOURCE: Drug Transport across the Blood-Brain Barrier (1997), 137-147. Editor(s): De Boer, Albertus G.; Sutanto, Win. Harwood: Amsterdam, Neth.
CODEN: 64JBAG
DOCUMENT TYPE: Conference
LANGUAGE: English
AB One of the most sensitive and versatile methods to measure drug passage through the blood-brain barrier (BBB) is microdialysis. In this study, microdialysis measurements of SDZ ICM 567, a new **5-HT3** receptor **antagonist** with a potential efficacy against various central nervous system (**CNS**) **disorders**, were carried out in different brain areas and jugular vein of freely moving rats.

L7 ANSWER 3 OF 10 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 97163892 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9010647
TITLE: The non-antiemetic uses of serotonin 5-HT3 receptor antagonists. Clinical pharmacology and therapeutic applications.
AUTHOR: Greenshaw A J; Silverstone P H
CORPORATE SOURCE: Department of Psychiatry, University of Alberta, Edmonton, Canada.. andy.greenshaw@ualberta.ca
SOURCE: Drugs, (1997 Jan) 53 (1) 20-39. Ref: 188
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704

ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970401

AB The discovery of multiple subtypes of the serotonin 5-HT receptor has generated enormous interest over the past few years. Possibly the most exciting, in terms of psychiatric clinical practice, appeared to be the 5-HT3 receptor. Early animal studies suggested that the **5-HT3** receptor **antagonists**, in addition to their well recognised antiemetic use, might be clinically useful in a number of areas. These included anxiety disorders, psychotic disorders, drug and alcohol abuse disorders, depressive disorders, cognitive disorders, the treatment of pain and the treatment of irritable bowel syndrome. With the exception of antiemetic actions, this review examines these potential therapeutic areas carefully, paying particular attention not only to the animal literature, but to the clinical studies which have resulted from these initial findings. Unfortunately, studies in many of these therapeutic areas have not lived up to their initial promise. Indeed, no clinical studies have yet clearly demonstrated the usefulness of **5-HT3** receptor **antagonists** in the treatment of **CNS disorders**. Nonetheless, in view of the absence of published results from double-blind, placebo-controlled studies in many of these therapeutic areas, further research would be useful in confirming the effectiveness, or otherwise, of this group of compounds.

L7 ANSWER 4 OF 10 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 97081306 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9118822
TITLE: Ondansetron. A review of its pharmacology and preliminary clinical findings in novel applications.
AUTHOR: Wilde M I; Markham A
CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand.
SOURCE: Drugs, (1996 Nov) 52 (5) 773-94. Ref: 185
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 19970506
Entered Medline: 19970422

AB The use of ondansetron, a selective serotonin **5-HT3** receptor **antagonist**, is well established in patients with nausea and vomiting associated with cancer chemotherapy, radiotherapy or anaesthesia and surgery. The wide distribution of 5-HT3 receptors in the body and the role of these receptors in disease have provided the rationale for investigation of ondansetron in novel applications. Preliminary data have shown ondansetron to have clinical benefit in patients with nausea and vomiting associated with drug overdosage or poisoning, anti-infective or antidepressant therapies, uraemia or neurological trauma, and in patients with pruritus. Patients with gastrointestinal motility disorders (e.g. carcinoid syndrome, irritable bowel syndrome, diarrhoea associated with cryptosporidiosis or diabetes, and chronic refractory diarrhoea) have also shown some improvement when treated with ondansetron, as have patients with certain pain or **CNS**-related **disorders** [e.g. alcohol (ethanol) dependence, opiate withdrawal, vertigo, cerebellar tremor and Parkinson's disease treatment-related psychosis]. In contrast to conventional antiemetics, ondansetron is generally well tolerated with a lower incidence of sedation and only isolated case reports of extrapyramidal reactions. Furthermore, unlike dopamine receptor-blocking neuroleptics, ondansetron does not appear to worsen the symptoms of Parkinson's disease. Thus, in addition to its established indications, preliminary results suggest that ondansetron may be beneficial in a number of novel applications. This drug may represent a treatment alternative in patients with refractory disease, or an effective treatment of conditions for which

current therapies are either poorly tolerated or not available. Further investigation of ondansetron in a range of potential new applications appears to be warranted.

L7 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:762440 CAPLUS
DOCUMENT NUMBER: 123:160051
TITLE: Measurement of Free concentration of SDZ ICM 567 in blood and muscle using microdialysis sampling
AUTHOR(S): van Amdsterdam, C.; Boukhabza, A.; Ofner, B.; Pacha, W.; Lemaire, M.
CORPORATE SOURCE: Department of Drug Metabolism and Pharmacokinetics, Sandoz Pharma Ltd., Basel, CH-4002, Switz.
SOURCE: Biopharmaceutics & Drug Disposition (1995), 16(6), 521-7
CODEN: BDDID8; ISSN: 0142-2782
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In pharmacokinetics, the unbound drug concentration in interstitial tissue fluid has been conventionally postulated to be the same as the unbound drug concentration in blood (free-ligand hypothesis). Free drug mols. are well known to be the main determinant for pharmacol. response, but only restricted information concerning their concns. in most tissues is available. This was often due to a lack of suitable in vivo sampling methods. Recently, microdialysis has become an important tool for measuring the amount of exogenous and endogenous compds. in various tissues, e.g. brain, liver, and lung. Protein-bound drug is excluded from uptake into the probe by the dialysis membrane. Thus, microdialysis probes placed in blood and tissue permit direct and continuous measurement of unbound drug concentration with time. A previous study utilizing this technique was undertaken to examine the brain and blood pharmacokinetics of SDZ ICM 567 (Sandoz Pharma Ltd., Basel, Switzerland), the 7-methoxy derivative of tropisetron. SDZ ICM 567 has a mol. weight of 314 and is a new **5-HT3** receptor **antagonist** with potential efficacy against multiple **CNS disorders**. It was found that blood levels of the unbound drug exceeded those in brain by a factor of approx. five. This disposition, not in agreement with the passive diffusion concept, was related to an active transport mechanism for SDZ ICM 567 out of the brain. The aim of this study was to analyze the diffusion of unbound SDZ 1CM 567 in a tissue different from brain; thus, microdialysis was used to quantify the distribution of SDZ ICM 567 into rat muscle in comparison to blood concns. Transport and distribution consistent with the free-ligand hypothesis would result in an unbound tissue level equal to that measured in the systemic circulation. The microdialysis method used in this study clearly demonstrated the validity of the free-ligand theory in the muscle compartment, thus supporting the hypothesis of an active transport of SDZ ICM 567 between brain and blood.

L7 ANSWER 6 OF 10 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 4
ACCESSION NUMBER: 95143020 EMBASE
DOCUMENT NUMBER: 1995143020
TITLE: Therapeutic potential of serotonin 5-HT3 antagonists in neuropsychiatric disorders.
AUTHOR: Bentley K.R.; Barnes N.M.
CORPORATE SOURCE: Department of Pharmacology, Medical School, University of Birmingham,Edgbaston, Birmingham B15 2TT, United Kingdom
SOURCE: CNS Drugs, (1995) 3/5 (363-392).
ISSN: 1172-7047 CODEN: CNDREF
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Serotonin 5-HT3-receptors are the only monoamine neurotransmitter

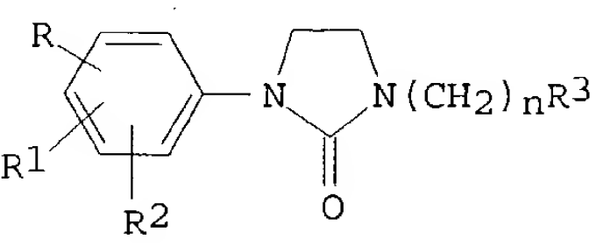
receptors that are a member of the ligand-gated ion channel receptor superfamily, enabling these receptors to modulate fast synaptic transmission. Over the past 10 years, 5-HT3-receptors have been extensively investigated. Whilst it is generally accepted that **5-HT3**-receptor **antagonists** attenuate emesis induced by a variety of stimuli, an extensive body of evidence indicates that these ligands may also alleviate some of the symptoms associated with various **CNS disorders** (e.g. psychosis, anxiety, dementia) and also reduce the rewarding properties of and withdrawal symptoms associated with drugs of abuse. In general, however, the clinical potential described for **5-HT3**-receptor **antagonists** has not been substantiated by a number of preclinical and clinical reports. The further unravelling of the mechanisms underlying the actions of **5-HT3**-receptor **antagonists**, and the reasons why they apparently fail to display efficacy in the hands of some experienced investigators, remain major objectives for the future.

L7 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:508793 CAPLUS
DOCUMENT NUMBER: 121:108793
TITLE: Phenylimidazolidinone derivatives, process for their preparation and their use as 5-HT3 receptor antagonists
INVENTOR(S): Varasi, Mario; Heidempergher, Franco; Caccia, Carla; Arrigoni, Claudio
PATENT ASSIGNEE(S): Farmitalia Carlo Erba S.r.l., Italy
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9411347	A1	19940526	WO 1993-EP2924		19931022
W: AU, BY, CA, FI, HU, JP, KR, KZ, NZ, PL, RU, UA					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2127536	AA	19940526	CA 1993-2127536		19931022
AU 9453364	A1	19940608	AU 1994-53364		19931022
AU 666793	B2	19960222			
EP 623114	A1	19941109	EP 1993-923529		19931022
EP 623114	B1	19990506			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE					
JP 07503256	T2	19950406	JP 1993-511639		19931022
HU 70395	A2	19951030	HU 1994-1948		19931022
IL 107371	A1	19980208	IL 1993-107371		19931022
PL 174416	B1	19980731	PL 1993-304676		19931022
RU 2126403	C1	19990220	RU 1994-36775		19931022
AT 179701	E	19990515	AT 1993-923529		19931022
ES 2133415	T3	19990916	ES 1993-923529		19931022
US 5424328	A	19950613	US 1993-144514		19931102
ZA 9308206	A	19940610	ZA 1993-8206		19931103
CN 1093702	A	19941019	CN 1993-114768		19931117
FI 9403376	A	19940715	FI 1994-3376		19940715
PRIORITY APPLN. INFO.:			GB 1992-24144	A	19921118
			WO 1993-EP2924	W	19931022

OTHER SOURCE(S): MARPAT 121:108793
GI



I

AB Title compds. I (n = 1-3; R, R1, R2 = H, halo, HO, NC, C1-6 alkyl, F3C, C1-6 alkoxy, C1-6 alkylthio, CHO, C2-6 alkanoyl, HO2C, C1-6 alkoxycarbonyl, O2N, R4R5N wherein R4, R5 = H, C1-6 alkyl, CHO, C2-6 alkanoyl, R7R6NSO2 wherein R6, R7 = H, C1-6 alkyl; R3 (substituted)imidazolyl) or a salt thereof, are prepared I are claimed to be useful in treatment of **CNS disorders**, anti-anxiety, anti-emesis, cognition activator, anti-drug addiction agent and in treatment of gut motility disorders, and migraine (no data). To 1-(3-chlorophenyl)imidazolidin-2-one was added NaH followed by 4-(chloromethyl)-5-methyl- 1-(triphenylmethyl)-1H-imidazole to give I [RR1R2 = 3-Cl, R3 = 5-methyl-1-(triphenymethyl)-1H-imidazolyl, n = 1] which was deprotected to give I (RR1R2 = 3-Cl, R3 = 5-methyl-1H-imidazol-4-yl, n = 1) (II) which at 10 μg/kg i.v. showed in vivo **5-HT3 antagonist** activity of 89.7%. Tablet and capsule formulations comprising II are given.

L7 ANSWER 8 OF 10 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 94025300 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8105596
TITLE: Behavioural pharmacology of 5-HT3 receptor antagonists: a critical update on therapeutic potential.
AUTHOR: Greenshaw A J
CORPORATE SOURCE: Department of Psychiatry, University of Alberta, Edmonton, Canada.
SOURCE: Trends in pharmacological sciences, (1993 Jul) 14 (7) 265-70. Ref: 54
Journal code: 7906158. ISSN: 0165-6147.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19980206
Entered Medline: 19931109

AB There has been tremendous interest in **5-HT3** receptor **antagonists** since their discovery and the subsequent identification of 5-HT3 receptors in the CNS. Based on the results of early behavioural tests with these compounds, there has been substantial interest in their potential use for the treatment of various **CNS disorders**. In this review, Andrew Greenshaw attempts to clarify the status of the therapeutic potential of these drugs, discussing inconsistencies in preclinical findings and identifying areas in need of clarification through future research. **5-HT3** receptor **antagonists** are claimed to be potentially useful in the treatment of nausea, inflammatory pain (migraine and irritable bowel syndrome), anxiety, depression, schizophrenia, dementia and drug abuse!

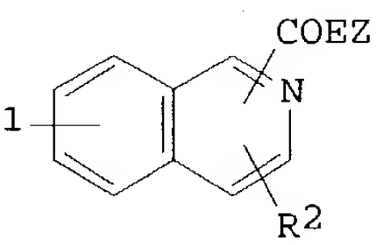
L7 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:128687 CAPLUS
DOCUMENT NUMBER: 116:128687
TITLE: Preparation of isoquinolinecarboxamides and -carboxylates as 5-HT3 antagonists
INVENTOR(S): King, Francis David
PATENT ASSIGNEE(S): Beecham Group PLC, UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9117161	A1	19911114	WO 1991-GB636	19910422

W: AU, CA, JP, KR, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

AU 9177539	A1	19911127	AU 1991-77539	19910422
EP 526545	A1	19930210	EP 1991-908698	19910422
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05507071	T2	19931014	JP 1991-508211	19910422
ZA 9103123	A	19920527	ZA 1991-3123	19910425
RIORITY APPLN. INFO.:			GB 1990-9542	19900427
			WO 1991-GB636	19910422

THER SOURCE(S): MARPAT 116:128687
I



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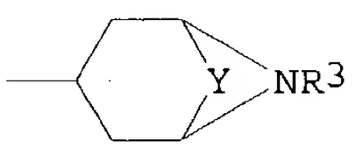

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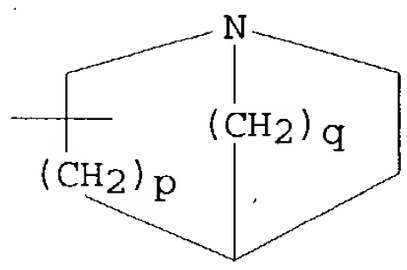

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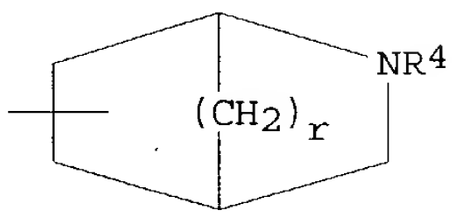

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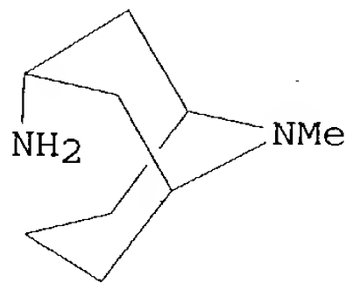

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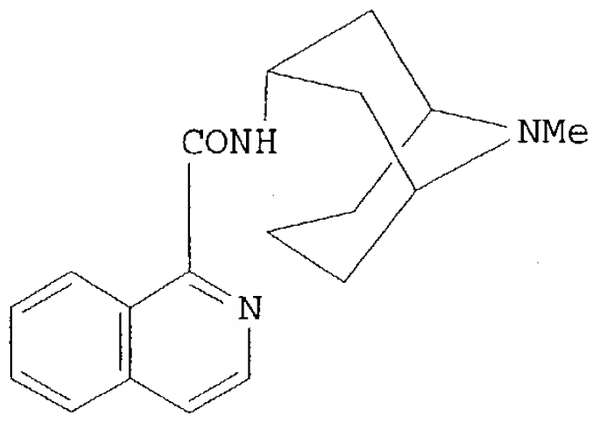

III

B The title compds. [I; R1 = H, halo, alkyl, alkoxy, OH, NO2; R2 = H, alkyl, alkoxy at 3-position, CF3, acyl, (substituted) Ph, etc. at 4-position; E = NH, O; Z = Q, Q1, Q2 wherein R3, R4 = H, C1-4 alkyl; Y = CH2XCH2; X = CH2, O, S, bond; p = 1, 2; q, r = 1-3], **5-HT3 antagonists** (no data) useful in the treatment and prophylaxis of pain, emesis, **CNS disorders**, and gastrointestinal **disorders**, are prepared A solution of isoquinoline-1-carboxylic acid 2, N-hydroxysuccinimide 1.5, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide 2.6 g in DMF was stirred at room temperature, cooled to 0°, and treated with a solution of 2 g amine II in CH2Cl2 at room temperature to give 2.4 g title amide III. Also prepared were addnl. I.

7 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6

CCESSION NUMBER:	1990:172140 CAPLUS
OCUMENT NUMBER:	112:172140
ITLE:	Effect of 5-HT3 receptor antagonists on responses to selective activation of mesolimbic dopaminergic pathways in the rat
UTHOR(S):	Hagan, R. M.; Jones, B. J.; Jordan, C. C.; Tyers, M. B.
ORPORATE SOURCE:	Dep. Neuropharmacol., Glaxo Group Res. Ltd., Ware/Hertfordshire, SG12 0DP, UK
OURCE:	British Journal of Pharmacology (1990), 99(2), 227-32 CODEN: BJPCBM; ISSN: 0007-1188
OCUMENT TYPE:	Journal
ANGUAGE:	English

The effects of 5-hydroxytryptamine3 (**5-HT3**) receptor **antagonists** on the behavioral hyperactivity response which results from injection of the neurokinin receptor agonist [pGlu5, MePhe8, Sar9]-substance P (5-11) (DiMe-C78) into the ventral tegmental area (VTA) of the rat midbrain have been determined S.c. administration of ondansetron (GR38032) (0.001-0.3 mg/kg), GR65630 (0.01 mg/kg), ICS 205-930 (0.1 mg/kg) and MDL 72222 (0.1 mg/kg), inhibited the DiMe-C7-induced hyperactivity response. The effects of ondansetron on DiMe-C7-induced changes in dopamine and 5-HT metabolism in discrete areas of rat forebrain were studied in order to investigate further the possible mechanism of action of **5-HT3 antagonists** in modifying mesolimbic dopaminergic systems. Intra-VTA administration of DiMe-C7 increased levels of dihydroxyphenylacetic acid (DOPAC) in the nucleus accumbens, olfactory tubercules and right amygdala, indicating increased mesolimbic dopamine metab; DOPAC levels were not altered in any of these brain areas. DiMe-C7 also increased 5-hydroxyindoleacetic acid (5-HIAA) levels in the right amygdala. 5-HT levels were not changed by DiMe-C7 treatment. In control rats, pretreatment with ondansetron (0.1 mg/kg) had no effect on the levels of dopamine, 5-HT or their metabolites, but in rats given DiMe-C7, ondansetron inhibited the increase in DOPAC levels in the nucleus accumbens. These results are in agreement with the proposed facilitatory role of 5-HT3 receptor activation on mesolimbic dopaminergic transmission, and suggest that **5-HT3 antagonists** may have important therapeutic indication for the treatment of **CNS disorders** in which mesolimbic dopamine systems are perturbed.

5 ANSWER 43 OF 74 PCTFULL COPYRIGHT 2004 Univentio on STN
CCESSION NUMBER: 1993025555 PCTFULL ED 20020513
ITLE (ENGLISH): DERIVATIVES OF IMIDAZO [5,1-C][1, 4]BENZOXAZIN-1-ONE AS **5 HT3 ANTAGONISTS**
ITLE (FRENCH): DERIVES D'IMIDAZO(5,1-C)(1,4)BENZOXAZINE-1-ONE UTILISES COMME ANTAGONISTES DE 5HT3
NVENTOR(S): VARASI, Mario;
HEIDEMPERGHER, Franco;
ARRIGONI, Claudio;
CACCIA, Carla
ATENT ASSIGNEE(S): FARMITALIA CARLO ERBA S.R.L.
ANGUAGE OF PUBL.: English
OCUMENT TYPE: Patent
ATENT INFORMATION:

NUMBER	KIND	DATE
WO 9325555	A1	19931223

ESIGNATED STATES
W: AU BY CA FI HU JP KR KZ NZ PL RU UA AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
PPLICATION INFO.: WO 1993-EP1498 A 19930614
RIORITY INFO.: GB 1992-9212486.6 19920612

BEN The invention provides derivatives of 2,3,3a,4-tetrahydro-2-azabicyclo alkyl-1H-imidazo [5,
1-C][1,4]benzoxazin-1-one of general formula (I), in which inter alia R3 represents (a) or (b)
wherein n is an integer or 1 or 2 and R8 is hydrogen, C1-C6 alkyl unsubstituted or substituted by
phenyl, C2-C4 alkenyl, C2-C4 alkynyl, formyl or C2-C6 alkanoyl; and the pharmaceutically acceptable
salts thereof, which are useful in the treatment of **CNS disorders**, gut motility **disorders**, emesis
and migraine, as cognition activators, anti-drug addiction agents and analgesics.

ACCESSION NUMBER: 506545 EUROPATFULL EW 199853 FS PS
TITLE: Use of 4-amino-1-(2-pyridyl)piperidines as **5**-**HT3**-agonists for the treatment and prophylaxis of serotoninergic dysfunctions.
Verwendung von 4-Amino-1-(2-Pyridyl)Piperidinen als **5**-**HT3**-Agonisten zur Behandlung und Verhuetung von serotoninergen Dysfunktionen.
Utilisation de 4-amino-1-(2-pyridyl)piperidines comme agonistes **5**-**HT3** pour le traitement et la prophylaxie des dysfonctionnements serotoninergiques.

INVENTOR(S): Le Fur, Gerard, 19ter, rue des Carrieres, F-95160 Montmorency, FR;
Bianchetti, Alberto, Via Corridoni N.11, I-20122 Milan, IT;
Giudice, Antonina, Via Cenisio 61, I-20154 Milan, IT;
Croct, Tiziano, Via Messina N. 55, I-20122 Milan, IT;
Soubrie, Philippe, Le Rey - Valfaunes, I-34270 Saint Mathieu de Treviers, IT
PATENT ASSIGNEE(S): SANOFI, 174, avenue de France, 75013 Paris, FR, in BE, CH, DE, DK, FR, GB, LI, LU, NL, PT, SE, AT;
SANOFI WINTHROP S.p.A., Via Piranesi 38, 20137 Milano, IT, in IT
PATENT ASSIGNEE NO: 400327; 560092
AGENT: Gillard, Marie-Louise et al, Cabinet Beau de Lomenie 158, rue de l'Universite, 75340 Paris Cedex 07, FR
AGENT NUMBER: 15871
OTHER SOURCE: EPB1998070 EP 0506545 B1 981230
SOURCE: Wila-EPS-1998-H53-T1
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Franzoesisch; Veroeffentlichung in Franzoesisch
DESIGNATED STATES: R AT; R BE; R CH; R DE; R DK; R FR; R GB; R IT; R LI; R LU; R NL; R PT; R SE
PATENT INFO.PUB.TYPE: EPB1 EUROPAEISCHE PATENTSCHRIFT
PATENT INFORMATION:

PATENT NO	KIND	DATE
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REF. NON-PATENT-LIT.: NEUROCHEM. INT., vol. 16, no. 3, 1990, pages 309-312, Pergamon Press plc, GB; R.W. FULLER et al.: "Neurochemical effects of CM 57227 and CM 57373, two anorectic agents, on brain serotonin neurons in rats" DIALOG INFORMATION SERVICES, INC., File 155, Medline, AN=07215162; S. GARATTINI et al.: "Reduction of food intake by manipulation of central serotonin. Current experimental results", & BR. J. PSYCHIATRY SUPPL., DEC. 1989, (8), P 41-51 STN INTERNATIONAL, KARLSRUHE DE, FILE CA, CHEMICAL ABSTRACTS, vol. 111, no. 3, abrege no. 17620k, Columbus, Ohio, US; A.W. SCHMIDT et al.: "Antidepressant interactions with 5-hydroxytrytamine3 receptor binding sites", & EUR. J. PHARMACOL., 1989, 163(2-3), 397-8

DETDFR. . . EP-B-0021973 comme inhibant la capture (denommee "uptake" en anglais) de la serotonine, possedent une activite agoniste selective vis-a-vis des recepteurs **5**-**HT**.sub3. au niveau peripherique et central.
Plus . . . formule (I) ou R a la signification donnee ci-dessus et leurs sels pharmaceutiquement acceptables, ont une affinite pour les sites **5**-**HT**.sub3. nettement superieure a celle de la serotonine et de la 2-methylserotonine.

On . . . par des essais de binding ex vixo conduits sur des composes representatifs de cette classe, que l'affinite pour les sites **5**-**HT**.sub3. centraux est nettement superieure a celle pour les sites de capture ("uptake") de la serotonine.
Un . . . pathologies se rapportant aux troubles du SNC, dans lesquelles une action serotoninergique provenant de la mediation selective par les recepteurs **5**-**HT**.sub3.est demandee.
L'affinite des composes de formule (I') aux recepteurs **5**-**HT**.sub3. a ete evaluee d'abord par un test de binding in vitro en utilisant les sites de liaison **5**-**HT**.sub3.
presents dans le cortex cerebral du rat (cfr. G.J. Kilpatrick, B.J. Jones et M.B. Tyers. Identification and distribution of **5**-**HT**.sub3. receptors in rat brain using radioligand binding. Nature 1987; 330: 746-8) et comme ligand marque le [.sup3.H] BRL 43694 (granisetron), antagoniste puissant et specifique des recepteurs **5**-**HT**.sub3.. La puissance des composes de formule (I')
dans le deplacement du [.sup3.H] BRL 43694 a ete comparee a celle de la serotonine et a celle d'autres agonistes **5**-**HT**.sub3.
(2-methyl-serotonine et m-chlorophenylbiguanide), ainsi qu'a celle de l'antagoniste IC 205930.
Pour . . . la methode reportee par Nelson et Thomas (D.R. Nelson et D.R. Thomas. [.sup3.H] BRL 43694 (granisetron), a specific ligand for **5**-**HT**.sub3. binding sites in rat brain cortical membranes. Biochem. Pharmacol. 1989; 38: 1963-5). En resume, les cortex provenant de 4 animaux. . .
La cinetique d'association et de dissociation du [.sup3.H] BRL 43694 aux sites **5**-**HT**.sub3. a ete suivie pendant 45 minutes, respectivement en absence et en presence de ICS 205930, 1 μM).
Cette affinite pour les recepteurs **5**-**HT**.sub3. est tout a fait selective. En particulier, on a evalue la capacite du meme compose (CM 57227) a deplacer in. . . il apparait clairement des resultats obtenus que ce produit ne possede aucune affinite K.subi. > 10.000 nM) pour les recepteurs **5**-**HT**.sub1A. et **5**-**HT**.sub1B., pour le site d'uptake de la serotonine (deplacement de la [.sup3.H] paroxetine), pour les sites adrenergiques α.sub1., α.sub1., β.sub1. et. . .
Les . . . soumis a ce test ont montre une DI.sub50. (mg/kg i.p) comparable a celle du compose GR 38032 F, un antagoniste **5**-**HT**.sub3. selectif connu, utilise comme produit de reference.
Comme . . . 2-methyl-serotonine, le chlorhydrate de la 4-amino-1-(6-chloro-2-pyridyl)piperidine, injecte dans le striatum de souris, provoque des rotations ("turning") inhibees par les antagonistes **5**-**HT**.sub3.. Injecte par voie i.p., ce compose s'oppose a l'antagonisme exerce par l'ondansetron (1 mg/kg i.p.) vis-a-vis du "turning" induit par. . .
L'activite agoniste selective des recepteurs **5**-**HT**.sub3. des composes de formule (I') a ete confirmee in vivo dans le test de Bezold-Jarish. Dans ce test, l'administration par. . .
Cet effet est inhibe par les antagonistes selectifs des recepteurs **5**-**HT**.sub3. (par exemple ICS 205930 et zacopride), tandis qu'il n'est pas inhibe par les antagonistes des recepteurs D de la serotonine. . .
Les . . . formule (I') ou R' a la signification donnee ci-dessus ont montre aussi une activite procinetique intestinale liee a leur action **5**-**HT**.sub3. agoniste.
Cette activite est liee a l'activite **5**-**HT**.sub3. agoniste etant donne que les **5**-**HT**.sub3. antagonistes selectifs, comme la zacopride ou l'ICS 205930, l'antagonisent.
Sur . . . se rapportant aux troubles du SNC et en particulier des systemes serotoninergiques, provenant de la mediation selective par les recepteurs **5**-**HT**.sub3..
Les . . . ainsi que leurs sels pharmaceutiquement acceptables, sont donc des agents psychotropes potentiels tres interessants, pouvant agir par l'intermediaire des recepteurs **5**-**HT**.sub3..
En . . . utilises dans le traitement de toutes pathologies dans lesquelles une action serotoninomimetique provenant de la mediation selective par les recepteurs **5**-**HT**.sub3. peut etre benefique.

TIEN Use of 4-amino-1-(2-pyridyl)piperidines as **5-HT3** -agonists for the treatment and prophylaxis of serotoninergic dysfunctions.

TIDE Verwendung von 4-Amino-1-(2-Pyridyl)Piperidinen als **5-HT3**-Agonisten zur Behandlung und Verhuetung von serotoninergen Dysfunktionen.

TIFR Utilisation de 4-amino-1-(2-pyridyl)piperidines comme agonistes **5-HT3** pour le traitement et la prophylaxie des dysfonctionnements serotoninergiques.

CLMEN. . . pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment and the prophylaxis of pathologies related to **disorders** of the **CNS** in which a serotoninergic action selectively mediated by **5-HT** .sub3. receptors is required.

CLMDE. . . Krankheiten, die mit Stoerungen des Zentralnervensystems in Zusammenhang stehen, bei denen eine serotoninerge Wirkung, die von der selektiven Vermittlung durch **5-HT**.sub3.-Rezeptoren herruehrt, erforderlich ist.

CLMFR. . . pathologies se rapportant aux troubles du SNC, dans lesquelles une action serotoninergique provenant de la mediation selective par les recepteurs **5-HT**.sub3. est demandee.

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AB There has been tremendous interest in **5-HT3** receptor **antagonists** since their discovery and the subsequent identification of 5-HT3 receptors in the CNS. Based on the results of early behavioural tests with these compounds, there has been substantial interest in their potential use for the treatment of various **CNS disorders**. In this review, Andrew Greenshaw attempts to clarify the status of the therapeutic potential of these drugs, discussing inconsistencies in preclinical findings and identifying areas in need of clarification through future research. **5-HT3** receptor **antagonists** are claimed to be potentially useful in the treatment of nausea, inflammatory pain (migraine and irritable bowel syndrome), anxiety, depression, schizophrenia, dementia and drug abuse!